

REMARKS/ARGUMENTS

The Pending Claims

Claims 1-27 are pending and are directed to a liposome (claims 1-19, and 22-24), a composition comprising the liposome (claim 20), an agent comprising the liposome (claim 21), and a method of producing the liposome (claims 25-27).

Amendments to the Claims

Claims 1, 12, and 13 have been amended to clarify the claim language. The amendments to the claims are supported by the specification at, for example, paragraph 0045.

Claims 22-27 are new and are supported by the specification at, for example, paragraphs 0030-0043.

No new matter has been added by way of these amendments to the claims.

Summary of the Office Action

Claims 1-21 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 1-5, 7, 11-16 and 20-21 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Modi (U.S. Patent 6,193,997).

Claims 1-7 and 9-21 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Modi in view of Slater et al. (U.S. Patent Application Publication 2003-0133973).

Claims 1-5, 7, 8, and 11-21 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Modi in view of Tagawa et al. (EP 1170018).

Claims 1-21 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-10 and 12 of copending U.S. Patent Application No. 11/812,804.

Reconsideration of these rejections is hereby requested.

Discussion of the Indefiniteness Rejections

The Office contends that claims 1-21 are indefinite. In particular, the Office indicates that the language in claims 1 and 12 is unclear.

With regard to claim 1, the Office is unsure whether the phrase “which has a particle size of 300 nm or less and contains a triglycerol” refers to the internal cavity or the liposome. Claim 1, as amended, recites that the liposome has a particle size of 300 nm or less and contains a triglycerol.

With regard to claim 12, the Office is not clear whether the ligand and/or water-soluble polymer are inside or outside of the liposome. Applicants have amended claim 12, as well as claim 13, to indicate that the ligand is bound to the surface of the liposome.

Applicants believe that the claims, as amended, are sufficiently clear. Therefore, Applicants request that the indefiniteness rejections be withdrawn.

Discussion of the Anticipation Rejection

The Office contends that the Modi reference discloses a liposome with a particle size of 10 nm or less, which contains a ligand and triolein. The anticipation rejection is traversed for the following reasons.

The Modi reference discloses a “mixed liposome,” which is different from the liposome of the pending claims. For example, the “mixed liposome” of the Modi reference has a particle size of 1 to 10 nm and preferably 1 to 5 nm (see, e.g., column 5, lines 36-39, column 6, lines 42-44, column 7, lines 46-48, column 8, lines 44-48, and column 9, lines 15-16 and 61-62).

A liposome, such as that of the pending claims, has a lipid bilayer membrane generally having a thickness of 4 to 4.5 nm (see, e.g., *Liposome Technology* 2nd Edition, Volume 1: Liposome Preparation and Related Techniques, Ed. by Gregory Gregoriadis, Ph.D., CRC Press (1992), page 7, a copy of which is enclosed herewith). Thus, the diameter of a liposome includes 8 to 9 nm of lipid bilayer membrane, as well an inner sphere (i.e., internal cavity), whose diameter is greater than the thickness of the lipid bilayer membrane.

Accordingly, the particle size of a liposome is greater than that of the "mixed liposome" of the Modi reference.

Since the Modi reference does not disclose a liposome as required by the pending claims, the Modi reference does not anticipate the pending claims. Therefore, Applicants request that the anticipation rejection be withdrawn.

Discussion of the Obviousness Rejections

The Office contends that it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention in view of the Modi reference and either of the Slater or Tagawa references. The obviousness rejections are traversed for the following reasons.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Consideration of the aforementioned *Graham* factors here indicates that the present invention, as defined by the pending claims, is unobvious in view of the cited references.

As regards the scope and content of the prior art, the Office contends that the Modi reference discloses a liposome comprising a triglycerol (triolein), wherein the particle size of the liposome is 10 nm or less. The Office acknowledges that the Modi reference does not disclose that the internal cavity of the liposome comprises a compound and a polysaccharide, the particular compounds recited in claims 9, 10, 17, and 18, or a polymer bound to the external surface of the liposome.

The Office relies on the Slater reference for its disclosure of liposomes with hydrophilic polymer chains on the outside of the liposomes and polyanionic polymers (e.g., sulfate polysaccharides, hyaluronic acid, chondroitin sulfate, celluloses, and cellulose derivatives) entrapped in the liposomes.

The Office relies on the Tagawa reference for its disclosure of ligand-bonded complexes, wherein the ligand is bonded through a water-soluble macromolecule, such as polyalkylene glycol or polyethylene glycol. Additionally, the Office contends that the Tagawa reference discloses that anti-tumor agents, such as cisplatin, can be encapsulated in the liposome.

The Office considers that it would have been obvious for one of ordinary skill in the art to use the compounds disclosed in the Slater or Tagawa reference in a liposome as taught by the Modi reference.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

The present invention, as defined by the pending claims, is directed to a liposome encapsulating a water-soluble substance in an internal cavity thereof, wherein the liposome has a particle size of 300 nm or less and contains a triglycerol, as well as a method of producing such a liposome.

As discussed above, the Modi reference discloses a "mixed liposome," which differs from the inventive liposome and those disclosed in the Slater and Tagawa references based on particle size. The "mixed liposome" has a particle size of 10 nm or less. In contrast, the Slater reference discloses liposomes with particles sizes of 40-250 nm (see, e.g., paragraph 82 of the Slater reference), and the Tagawa reference discloses liposomes with particles sizes of 20-500 nm (see, e.g., paragraphs 22-23 of the Tagawa reference). Accordingly, the Modi reference and the Slater and Tagawa references are directed to two different products ("mixed liposomes" versus conventional liposomes), such that one of ordinary skill in the art would not have had any reason to combine the disclosures of these references, let alone in the particular manner that would result in the claimed invention.

Furthermore, the existence of unexpected benefits attendant the present invention rebuts the obviousness rejections.

It was known that a liposome with a smaller particle size has advantageous properties in pharmacokinetics, such as higher retention in blood and higher accumulation in a tumor; however, liposomes with a smaller particle size have the problem of smaller capacity of drug encapsulation due to a smaller volume of aqueous phase encapsulated in an inner sphere space of the liposome. Additionally, liposomes with a smaller particle size have the problem of thermodynamic instability, such that difficulty arises in the preparation of a liposome with smaller particle size in uniform quality.

The inventors discovered, however, that by using triglycerol as one of the liposome-forming lipids, an unexpected and advantageous improvement on the stability of the liposome results relative to the liposomes known in the art. Additionally, particle size variation is significantly reduced, which results in the ability to avoid contamination with liposomes of larger particle size. Moreover, a higher rate of drug encapsulation into the liposome is achieved with use of the inventive liposome. The advantageous results achieved using the inventive liposome were unexpected given the teachings in the art.

The existence of the unexpected benefits attendant the present invention rebut the obviousness position recited in the Office Action, even if the combination of the disclosures of the cited references are considered to properly establish *prima facie* obviousness.

Considering all of the *Graham* factors together, it is clear that the present invention – as defined by the pending claims – would not have been obvious to one of ordinary skill in the art at the relevant time in view of the Modi reference alone or in combination with the Slater and/or Tagawa references. Accordingly, the obviousness rejections should be withdrawn.

Discussion of the Provisional Nonstatutory Obviousness-Type Double Patenting Rejections

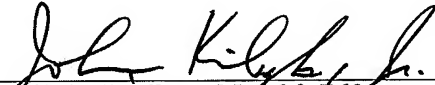
The Office provisionally rejects claims 1-21 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-10 and 12 of co-pending U.S. Patent Application No. 11/812,804 (“the ‘804 application”).

Applicants note that the claims of the '804 application do not teach or suggest the use of triglycerol as one of the membrane lipids for the preparation of a liposome. As discussed above, the use of triglycerol has surprising advantageous effects on the properties of the resulting liposome. Accordingly, the subject matter of the pending claims cannot be considered to be obvious in view of the claims of the '804 application. For these reasons, Applicants request that the provisional obviousness-type double patenting rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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